REMARKS

Claims 108-134, 137-139, 142-160, 211-235, and 297-318 are pending and stand rejected. Claims 211, 297, and 298 are objected to. Claims 108, 119, 120, 159, 160, 211, 297, 298, and 304 have been amended. No new matter has been introduced. Reconsideration and allowance of Claims 108-134, 137-139, 142-160, 211-235 and 297-318, are respectfully requested.

The Objection to Claims 211, 297, and 298

Claims 211, 297, and 298 are objected to for misspelling the term "organisms." Claims 211, 297, and 298 have been amended to correct the spelling of the term "organisms." Accordingly, removal of the objection to Claims 211, 297 and 298 is respectfully requested.

The Rejection of Claims 119-121 and 304 Under 35 U.S.C. § 112, Second Paragraph

Claims 119-121 and 304 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. The Examiner has taken the position that the term "associated with" in Claims 119, 120, and 304 is a relative term which renders the claim indefinite. Claim 121 is rejected for depending on Claim 120.

While not acquiescing with the Examiner's position, but in order to facilitate prosecution, Claims 119, 120, and 304 have been amended to replace the term "associated with" with the phrase "having a correlated occurrence across a population." Support for this amendment is found throughout the specification as filed, for example, at page 148, lines 16-26. Accordingly, removal of this ground of rejection for Claims 119-121 and 304 is respectfully requested.

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<u>The Rejection of Claims 108-134, 137-139, 142-160, 211-235 and 297-318 Under 35 U.S.C. § 102(e) as Being Anticipated by U.S. 2006/0111849 (Schadt et al.)</u>

Claims 108-134, 137-139, 142-160, 211-235 and 297-318 stand rejected under 35 U.S.C. § 102(e) as being anticipated by U.S. Patent Publication No. 2006/0111849 (Schadt et al.). Applicants respectfully traverse this ground of rejection for at least the following reasons.

While not acquiescing to the Examiner's position, but in order to facilitate prosecution, independent Claims 108, 159, 160, 211, 297, and 298 have been amended as follows:

Claim 108 has been amended and now recites:

A method for determining whether a first trait T_1 is causal for, <u>reactive to, or independent of</u> a second trait T_2 in a plurality of organisms of a species, the method comprising:

(A) identifying one or more loci in the genome of said species, wherein each locus Q of said one or more loci is a site of colocalization for (i) a respective quantitative trait locus (QTL_1) that is genetically linked to a variation in the first trait T_1 across the plurality of organisms and (ii) a respective quantitative trait locus (QTL_2) that is genetically linked to a variation in the second trait T_2 across said plurality of organisms; and

(B) determining whether said first trait T_1, is causal for, <u>reactive to, or independent of</u>, said second trait T_2, comprising testing, for each respective locus Q of said one or more loci identified in step (A), whether (i) a genetic variation Q^* of said respective locus Q across said plurality of organisms and (ii) said variation in said second trait T_2 across said plurality of organisms are correlated conditional on said variation in said first trait T_1 across said plurality of organisms,

wherein, when the genetic variation of (i) one or more loci Q tested in (B), and (ii) said variation in said second trait T_2 across said plurality of organisms are correlated conditional on said variation in said first trait T_1 across said plurality of organisms, said first trait T_1 is determined to be causal for, <u>and not reactive or independent of,</u> said second trait T_2, wherein step (B) is performed by a suitably programmed computer.

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Claim 159 has been amended and now recites:

A computer program product for use in conjunction with a computer system, the computer program product comprising a computer readable storage medium and a computer program mechanism embedded therein, the computer program mechanism comprising:

a T_1/T_2 overlap module that comprises instructions for identifying one or more loci in the genome of a species, wherein each locus Q of said one or more loci is a site of colocalization for (i) a respective quantitative trait locus (QTL_1) that is genetically linked to a variation in a first trait T_1 across a plurality of organisms in said species and (ii) a respective quantitative trait locus (QTL_2) that is genetically linked to a variation in a second trait T_2 across said plurality of organisms; and

a causality test module, for determining whether said first trait T_1 is causal for, reactive to, or independent of said second trait T_2 that comprises instructions for testing, for one or more locus Q of said one or more loci, whether (i) a genotype random variable Q^* of the respective locus Q across the plurality of organisms and (ii) said variation in the second trait T_2 across the plurality of organisms are correlated conditional on the variation in said first trait T_1 across the plurality of organisms.

Claim 160 has been amended and recites:

A computer system comprising:

a central processing unit;

a memory, coupled to the central processing unit, the memory storing an Q_1/Q_2 overlap module and a causality test module; wherein

the T_1/T_2 overlap module comprises instructions for identifying one or more loci in the genome of a species, wherein each locus Q of said one or more loci is a site of colocalization for (i) a respective quantitative trait locus (QTL_1) that is genetically linked to a variation in the first trait T_1 across a plurality of organisms of said species and (ii) a respective quantitative trait locus (QTL_2) that is genetically linked to a variation in the second trait T_2 across said plurality of organisms; and

a causality test module for determining whether said first trait T_1 is causal for, reactive to, or independent of, said second trait T_2 that

comprises instructions for testing, for one or more loci Q in the at least one locus, whether (i) a genotype random variable Q_* for the respective locus Q across the plurality of organisms and (ii) said variation in said second trait T_2 across said plurality of organisms are correlated conditional on the variation in the first trait T_1 across said plurality of organisms.

Claim 211 has been amended and now recites:

A method for determining whether a first trait T_1 is causal for, reactive to, or independent of a second trait T_2 in a plurality of organisms of a species, the method comprising:

(A)   identifying a locus Q in the genome of said species that is a site of colocalization for (i) a quantitative trait locus (QTL_1) that is genetically linked to a variation in the first trait T_1 across all or a portion of the plurality of organisms and (ii) a quantitative trait locus (QTL_2) that is genetically linked to a variation in the second trait T_2 across all or a portion of said plurality of organisms;

(B)   quantifying a first coefficient of determination between (i) a genetic variation Q^* of said locus Q across all or a portion of said plurality of organisms and (ii) said variation in said first trait T_1 across all or a portion of said plurality of organisms; and

(C)   quantifying a second coefficient of determination between (i) said genetic variation Q^* of said locus Q across all or a portion of said plurality of ~~organsisms~~ organisms and (ii) said variation in said first trait T_1 across all or a portion of said plurality of ~~organsims~~ organisms, after conditioning on said variation in said second trait T_2 across all or a portion of said plurality of organisms, wherein

said first trait T_1 is deemed to be causal for, and not reactive to, or independent of, said second trait T_2 when said first coefficient of determination is other than zero and said second coefficient of determination cannot be distinguished from zero, wherein at least one of steps (A) or (B) is performed by a suitably programmed computer.

Claim 297 has been amended and now recites:

A computer program product for use in conjunction with a computer system, the computer program product comprising a computer readable storage medium and a computer program mechanism embedded therein, the computer program mechanism for determining whether a first trait T_1 is causal for, reactive to, or independent of, a second trait T_2 in a plurality of organisms of a species, the computer program mechanism comprising:

(A)   instructions for identifying a locus Q in the genome of said species that is a site of colocalization for (i) a quantitative trait locus (QTL_1) that is genetically linked to a variation in the first trait T_1 across all or a portion of the plurality of organisms and (ii) a quantitative trait locus (QTL_2) that is genetically linked to a variation in the second trait T_2 across all or a portion of said plurality of organisms;

(B)   instructions for quantifying a first coefficient of determination between (i) a genetic variation Q^* of said locus Q across all or a portion of said plurality of organisms and (ii) said variation in said first trait T_1 across all or a portion of said plurality of organisms; and

(C)   instructions for quantifying a second coefficient of determination between (i) said genetic variation Q^* of said locus Q across all or a portion of said plurality of ~~organsisms~~ organisms and (ii) said variation in said first trait T_1 across all or a portion of said plurality of ~~organsims~~ organisms, after conditioning on said variation in said second trait T_2 across all or a portion of said plurality of organisms, wherein

said first trait T_1 is deemed to be causal for, and not reactive to or independent of, said second trait T_2 when said first coefficient of determination is other than zero and said second coefficient of determination cannot be distinguished from zero.

Claim 298 has been amended and now recites:

A computer system comprising:

a central processing unit;

a memory, coupled to the central processing unit, the memory comprising:

(A)   instructions for identifying a locus Q in the genome of said species that is a site of colocalization for (i) a quantitative trait locus (QTL_1) that is genetically linked to a variation in the first trait T_1 across

all or a portion of the plurality of organisms and (ii) a quantitative trait locus (QTL$_2$) that is genetically linked to a variation in the second trait T$_2$ across all or a portion of said plurality of organisms;

(B) instructions for quantifying a first coefficient of determination between (i) a genetic variation Q* of said locus Q across all or a portion of said plurality of organisms and (ii) said variation in said first trait T$_1$ across all or a portion of said plurality of organisms; and

(C) instructions for quantifying a second coefficient of determination between (i) said genetic variation Q* of said locus Q across all or a portion of said plurality of ~~orgrnsisms~~ organisms and (ii) said variation in said first trait T$_1$ across all or a portion of said plurality of ~~organsims~~ organisms, after conditioning on said variation in said second trait T$_2$ across all or a portion of said plurality of organisms, wherein

said first trait T$_1$ is deemed to be causal for, and not reactive to or independent of, said second trait T$_2$ when said first coefficient of determination is other than zero and said second coefficient of determination cannot be distinguished from zero.

Support for these amendments is found throughout the specification as filed, published as WO 2005/017652, for example, at page 3, lines 15-26 (summary of invention); page 12, line 21 to page 14, line 11; page 24, line 30 to page 25, line 16, FIGURES 2 and 3A-E; page 31, lines 26-29; page 32, line 5 to page 35, line 13; page 55, lines 16-26 and page 57, line 27 to page 62, line 13.

For example, the summary of the invention at page 3, lines 15-26, states:

Systems and methods for identifying genes that affect complex traits are provided. Advantageously, such systems and methods are not restricted to identifying causative genes within regions shared by cis-acting eQTL and cQTL. Instead, they make use of gene expression cis- and trans-acting QTL information as well as disease trait QTL information in order to identify cellular constituents that are under the control of the disease QTL. In other words, the present invention provides a process for identifying cellular constituents whose abundances are modulated by a disease trait QTL, and that, in turn, modulate the disease trait in a causal fashion. Additionally, the present invention provides a process for identifying disease traits that are causal for variations in cellular constituent levels. In the former case the cellular constituents are causal

for the disease trait, whereas in the latter case the cellular constituents are reactive to the disease trait. (emphasis added)

As further described in the specification at page 55, lines 16-26:

The aim of the causality test is to distinguish between the relationships that indicate a cellular constituent is causal for the clinical trait (scenarios 302, 308, and 310 of Fig. 3A) from those that are reactive to, or independent of the disease trait (scenarios 304 and 306, respectively, of Fig. 3A). The test for causality involving QTL, cellular constituent abundance (e.g., gene expression) and disease trait data is based on the same conditional probabilities that underlie mutual information measures that form the basis of the more general Bayesian network reconstruction problems. See, for example, Pearl, 1983, Probabilistic Reasoning in Intelligent Systems: Networks of Plausible Inference, Morgan Kaufmann Publishers, Inc., San Francisco. The causality test assesses whether the QTL (Q) and the disease trait (T) are correlated conditional on the cellular constituent abundance trait (G). (emphasis added)

It is noted that independent Claims 108, 159, 160, 211, 297, and 298, as amended, are not anticipated by Schadt et al. because Schadt et al. does not teach all the limitations of the claims, as amended. For example, Schadt et al. does not teach a method of determining whether a first trait T_1 is causal for, reactive to, or independent of a second trait T_2, as claimed. Rather, Schadt et al. is generally directed to methods for combining gene expression data with genetics data to determine whether the eQTL and cQTL colocalize to the same locus in the genome of a species in order to elucidate biological pathways associated with traits. See Schadt et al. at paragraph [0017]. As further described in Schadt, at paragraph 0018, gene expression data is analyzed in order to verify that genes are involved in the same pathway, or whether a set of genes represents more than one biological pathway.
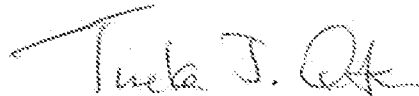
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Therefore, it is demonstrated that Claims 108, 159, 160, 211, 297, and 298, as amended, are not anticipated by Schadt et al. Accordingly, removal of this ground of rejection is respectfully requested.

Conclusion

Applicants believe that all of the pending claims are in condition for allowance. Reconsideration and favorable action are requested. If any issues remain that may be expeditiously addressed in a telephone interview, the Examiner is encouraged to telephone applicants' attorney at 206.695.1655.

Respectfully submitted,

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